

## Anxiety and cortisol levels during circumcision

Anxiety in circumcision

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### Abstract

**Aim:** In this study, we aimed to investigate whether circumcision is a stressor ambulatory surgical intervention for children and demonstrate the relationship between pre- and post-operative anxiety levels, blood cortisol levels (BCL), and salivary cortisol levels (SCL) in these children. **Material and Method:** Boys aged between 5 and 17 years, with a plan of circumcision, were prospectively included. Their preoperative anxiety levels, salivary cortisol levels (SCL), and blood total cortisol levels (BCL) were measured. After the operation, the same parameters were measured and preoperative values were compared with postoperative values. Also, the correlation between anxiety scores, SCL, and BCL was assessed. The Yale Preoperative Anxiety Scale was used to calculate the anxiety scores. **Results:** The mean age of 81 patients was  $6.62 \pm 1.40$  years. The preoperative anxiety scores, SCL, and BCL were significantly lower than post-operative values ( $p < 0.001$  for each). The preoperative SCL were positively correlated with BCL and anxiety scores. Postoperative SCL were positively correlated with BCL and anxiety scores. **Discussion:** Circumcision is a cause of increment in anxiety, serum, and salivary cortisol levels in children. Salivary cortisol levels were correlated with simultaneously drawn serum cortisol levels. The preoperative and postoperative anxiety scores were correlated with BCL and SCL in children with circumcision operation.

### Keywords

Anxiety Score; Circumcision; Salivary Cortisol; Serum Cortisol

## Introduction

Circumcision is the surgical removal of the foreskin of the penis. Motivation arising from either some personal or religious reasons makes the procedure prevalent in especially Muslim and Jewish populations. It is also one of the oldest surgical procedures, performed for medical indications, such as phimosis, balanitis xerotica obliterans, recurrent balanoposthitis, paraphimosis, and urine outlet obstruction, as well [1]. Recommendations of American Academy of Pediatrics, American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention, and World Health Organization are present, based on its long-term benefits which outweigh any risks [2].

Circumcision is performed as an ambulatory surgery, which can provide more improved patient satisfaction, reduced complications, and more efficient care. Anyway, as well as many other surgical procedures, circumcision is a source of anxiety, fear, and pain for children [3]. Increased preoperative anxiety levels result in negative consequences, such as challenges in the induction of anesthesia, increase in the need of anesthetic drugs during the operation and analgesic drugs after the operation, and increased risk of infections [4]. Following any surgical interventions and trauma, the stress response is triggered by impulses sent from the injured site to the hypothalamus. As well as activation of hypothalamic-pituitary-adrenal (HPA) axis, the serum levels of glucagon, catecholamines, and host of inflammatory cytokines are increased [5].

Total serum cortisol is the main parameter that is routinely measured in the assessment of HPA axis. Due to the changes in levels of the affinity of corticosteroid-binding globulin and misinterpreting in some patient groups, underestimation of the cortisol response in stress may happen [6]. Measuring salivary cortisol level (SCL) is a promising alternative, because of its strong correlation with serum-free cortisol, hence safe, easy, and non-invasive, and rapid method that is especially appropriate for pediatric patients [7]. Previously, SCL has been shown to reflect the stress in obstructive sleep apnea syndrome, dental caries, and burn wounds in children [8-10].

In this study, we aimed to investigate and confirm whether circumcision is a stressor ambulatory surgical intervention for children, and also we aimed to demonstrate the relationship between pre- and post-operative anxiety levels and blood and salivary cortisol levels in these children.

## Material and Methods

A prospective, observational study was planned to conduct in Erzurum Palandoken Government Hospital, between January 1, 2017 and December 31, 2017. Boys aged between 5 and 17 years, with a plan of circumcision, were included. Children with a known chronic disease (cardiac, respiratory, endocrinologic, and neurologic, etc.) and history of receiving any kind of corticosteroid therapy during the last month, were excluded. Local ethical committee approved the study protocol (Date:06/21/2016, Number: 2016/12-79) and the patients were included in the study after written informed consent was obtained from the parents of each child.

Preoperative anxiety levels of all children were calculated by means of the Yale Preoperative Anxiety Scale Modified – Short form (M-YPAS-SF), just 30 minutes before the surgery [11]. Additionally, salivary cortisol levels (SCL) and blood total cortisol levels (BCL) of all children were measured three times; between 08.00-13.00, on the day before the surgery (basal level); 30 minutes before the surgery (preoperative level); 2

hours after the surgery (postoperative level)

For sedation of the children, the protocol for anesthetic drugs was as follows: midazolam (after an initial intravenous dose (0.05 mg/kg), careful titration up to 0.4 mg/kg total dose was used (not exceeding 10 mg) until appropriate sedation and anxiolysis were achieved before the procedure); propofol (repeated bolus method; after an initial intravenous induction dose (2 mg/kg, 0.5 mg/kg) was given, additional bolus doses in every 3-5 minutes were applied until moderate sedation could be achieved).

No additional sedatives were used. During the monitorization, the duration of procedure, sedation, and recovery, and the doses of propofol and midazolam were recorded. And after the surgery, the Aldrete (recovery) scores were calculated [12]. Deep sedation/general anesthesia was defined as the state of blunted consciousness produced by anesthetic medications, resulting in partial loss of protective reflexes and purposeful responses to various stimuli [13]. During and after the surgery, complications such as apnea, O<sub>2</sub> desaturation, bradycardia, hypotension, cough, nausea, and vomiting were recorded and managed accordingly.

All SCL samples were drawn from the patients after at least 6 hours of fasting. For basal SCL samples, patients rinsed their mouth or drank water 10 minutes before sampling, between 08.00-13.00 am. Examination of cortisol levels (ng/ml) in saliva were performed in clarified saliva supernatants, which centrifuged (at 3500xg for 20 minutes) after sampling and stored at -80°C until analysis. ELISA kit (DRG Salivary Cortisol ELISA; DRG International, Inc., USA) was used following the manufacturer's instructions. BCLs were measured by Cobas e 601 (Roche Diagnostics GmbH; Mannheim, Germany). Blood samples were centrifuged (at 3500 rpm for 10 minutes) and serum samples were stored at -80°C until analysis.

The statistical analyses of the data of the present study were performed by means of IBM SPSS 20.0 software. The Kolmogorov-Smirnov test was used to evaluate the data distribution. To evaluate the changes in anxiety and cortisol levels, paired samples T-test was used to check differences before and after the surgery, at a significance level of 5% for normally distributed continuous variables. The correlation between anxiety, blood, and salivary cortisol levels was evaluated with the Pearson correlation test. Differences were considered significant if the p-value was < 0.05. Descriptive statistics were expressed as a mean ± SD.

## Results

Eighty-one patients were included in the study. Mean age of the patients was 6.62 ± 1.40 years. The data regarding the intra- and post-operative properties of the children were shown in Table 1. The preoperative anxiety scores, SCL, and BCL were significantly lower than post-operative values (p<0.001 for each) (Table-2). The pre-operative SCL were positively correlated with BCL and anxiety scores (Table 3). Similarly, post-operative SCL

**Table 1.** Intra- and post-operative properties of the children\*

Duration of sedation (min)	13.50±1.05
Duration of operation (min)	11.48±0.96
Duration of recovery (min)	4.58±1.17
Aldrete score	12.00±0
Dose of propofol (mg/kg)	90.60±19.32
Dose of midazolam (mg/kg)	1.48±0.31

\* Mean ± standard deviation

**Table 2.** Comparison of salivary cortisol, blood cortisol, and anxiety scores before and after surgery

	Before Surgery	After surgery	p
Salivary cortisol level (µg/ml)	0.320±0.22	0.589±0.35	<0.001
Blood cortisol level, (3-21 µg/dL)	5.934±4.19	9.360±6.10	<0.001
Anxiety Score	24.60±2.15	34.58±5.27	<0.001

**Table 3.** Correlation of salivary cortisol, blood cortisol, and anxiety scores before and after surgery\*

	Before Surgery			After surgery		
	Salivary Cortisol	Blood Cortisol	Anxiety Score	Salivary Cortisol	Blood Cortisol	Anxiety Score
Before Surgery	Salivary cortisol	1	0.88 <0.001*	0.54 <0.001*		
	Blood cortisol	0.88 <0.001*	1	0.46 <0.001*		
	Anxiety score	0.54 <0.001*	0.46 <0.001*	1		
After surgery	Salivary cortisol			1	0.86 <0.001*	0.52 <0.001*
	Blood cortisol			0.86 <0.001*	1	0.45 <0.001*
	Anxiety score			0.52 <0.001*	0.45 <0.001*	1

\*, all analyses were presented by r (correlation coefficient) and p (probability) values; \*, statistically significant

were positively correlated with BCL and anxiety scores. During and after the surgery, no serious complications, such as hypotension, arrhythmia, and cardiopulmonary arrest were experienced. Fifteen (18.5%) patients had a cough and 12 (14.8%) patients had nausea and vomiting in the post-operative period.

## Discussion

In this study, postoperative anxiety, blood, and salivary cortisol levels were higher than preoperative levels. It is expected that a surgical procedure can induce a physiological stress response. Nevertheless, an increased level of anxiety may reflect the surgical and anesthetic experience. Increased postoperative cortisol levels are assumed as instant values without long-term effects. A healthy and functional HPA axis has been proven in adulthood after circumcision [14]. Similar to this study, Hsu et al. [15] reported that sedation and anesthesia induced a significant rise in SCL in children, independent from the level of sedation or the type of procedure performed. Additionally, it was reported that preoperative anxiety of parent and child, the child's temperament, birth order, previous experience of hospitalization for surgery, preoperative premedication and preparation, the presence of parents at the induction of anesthesia and in the post-anesthetic care unit, or the different use of anesthetic drugs provided at induction in anesthesia may help to predict the postoperative anxiety of the children [3]. Anyway, general anesthesia without surgical intervention may not induce a stress response in children [16].

The measurement of hormones in saliva has been in development since the last decades. SCL is correlated with serum cortisol levels and displays a circadian rhythm similar to that of BCL, with a nadir at night and a peak level just after awakening [7]. Similarly, in this study, it was shown that preoperative SCL was correlated with preoperative BCL, while postoperative SCL was correlated with postoperative BCL. In a recent review, SCL has been proposed to assess cortisol excess,

deficiency and hydrocortisone replacement in clinical settings, having the advantage of detection when serum cortisol levels are low [17]. SCL has been shown to correlate with BCL in response to stress, similar to this study [18-20].

The anxiety of the children in this study was evaluated by modified YPAS, which included the assessments including the child's interaction with the environment, vocalization, expression of emotions, and interaction with family members [4]. The preoperative and postoperative anxiety scores were positively correlated with BCL and SCL in this study. It was noted that children who experience perioperative anxiety become prone to altered immunity, hence increased sensitivity to infections and subsequent consumption of analgesics postoperatively [21, 22]. These parameters were not studied because they were beyond the scope of this study. The use of SCL as a stress marker has been supported by previous studies [15, 23].

Although Jewish communities perform circumcision on the 8th day of life in accordance with the rules of Judaism given in Torah, many Muslims are circumcised in different ages [2]. The mean age of the study population was seen to correspond to the school ages. Younger ages could increase the risks of mental disorders, developmental delay, and attention deficit hyperactivity disorders, related to general anesthesia [24]. Additionally, greater behavioral distress and more pain, hence higher BCL and SCL would be experienced [25]. Nevertheless, this evaluation is beyond the scope of this study.

This study should be evaluated with accompanying limitations. Although the associations between the anxiety levels and cortisol levels were assessed, their association with anesthetic drug doses and durations of anesthesia and operation could not be evaluated. Anyway, this is a well-designed study to show an increased stress burden of circumcision, although it is a simple, ambulatory surgery.

As a conclusion, the results of this study have shown that circumcision induced an increment in anxiety, serum, and salivary cortisol levels in children. Salivary cortisol levels were in correlation with simultaneously drawn serum cortisol levels. Also, the preoperative and postoperative anxiety scores were correlated with BCL and SCL in children with circumcision operation.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

### Funding: None

### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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**How to cite this article:**

Kara D, Celik EC, Yesiltepe Y, Ozdemir F. Anxiety and cortisol levels during circumcision. *Ann Clin Anal Med* 2020;11(1):24-27